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# **A review of nutrient treatments for paediatric depression**

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## Abstract

Paediatric depression is estimated to affect 15 to 20% of youths prior to adulthood and is associated with significant social, educational and physical impairment. Current treatments comprise moderately efficacious psychological therapies and pharmaceutical antidepressants. However, nutritional therapies are also available and are regularly sought by people with depressive illnesses and parents of depressed youths. In this narrative review, studies examining the antidepressant effects of individual nutritional supplements in child and adolescent populations are appraised. Epidemiological studies examining the relationship between nutritional status and paediatric depression, or depressive symptoms are also reviewed. Nutrients covered in this article include: omega-3 polyunsaturated fatty acids, s-adenosylmethionine, vitamin C, vitamin D, zinc, iron and B-vitamins. Although several of these nutrients present as promising treatments for paediatric depression, there is a lack of high-quality studies examining the antidepressant effects of all the aforementioned ingredients. Before nutritional treatments are accepted as validated treatments for paediatric depression, further high-quality studies are required.

## Introduction

Paediatric depression is a debilitating psychological disorder that affects social, educational and physical function. It is experienced by approximately 2.8% of children and 5.7% of adolescents every year (Jane Costello et al., 2006). It is estimated that between 15 and 20% of youths will experience depression prior to adulthood (Birmaher et al., 1996; Merikangas et al., 2010). Depression during childhood is particularly concerning as there is a 70% chance of relapse within five years (Kovacs et al., 1984) and approximately 50% of children with a history of depression will experience a recurrence at least once during their adult life (Kessler et al., 2001; Melvin et al., 2013). Youth depression is also associated with several adverse outcomes during adulthood including suicidality, problems in social functioning, poor physical health, substance abuse and other mental health conditions including anxiety and eating disorders (Melvin et al., 2013).

Depression has a multifactorial etiology encompassing psychological, social, biological, and lifestyle factors, with treatment in paediatric populations primarily comprising psychological therapies (e.g., cognitive-behaviour therapy) and pharmaceutical antidepressants. In relation to pharmaceutical interventions, fluoxetine has gained approval for the treatment of childhood depression, although the use of other serotonin-reuptake inhibitors (SSRIs) and tricyclic antidepressants are often used (Wijlaars et al., 2012). Unfortunately, efficacy rates are disappointing with findings from several meta-analyses suggesting they provide only minimal-to-moderate benefit for the treatment of paediatric depression (Henry et al., 2012; Hetrick et al., 2012). Antidepressants also offer little-to-no benefit in enhancing overall well-being, self-esteem, and quality of life (Spielmans and Gerwig, 2014; Stevanovic et al., 2014). In addition, antidepressants are associated with an increased risk of suicidal ideation, leading to warnings regarding their potential to increase suicidal risk in youths (Hetrick et al., 2012; Julious, 2013).

Throughout adulthood, nutritional and herbal remedies are regularly used by depressed patients to alleviate depressive symptoms (Wu et al., 2007). Investigations into the role of diet in depression have confirmed important associations. In several meta-analyses on adult populations, consuming a Western diet (i.e., low-quality diet characterised by a high consumption of processed foods, such as fast food, processed meats, refined grains, soft drinks and sweets/ sugars) was associated with an increased odds of depression; while consuming a healthy, Mediterranean-based diet (i.e., high intake of fruit, vegetables, legumes, whole-grain products, and fish; and a low-to-moderate intake of meat, dairy products and alcohol) was associated with a reduced odds of depression (Lai et al., 2014; Psaltopoulou et al., 2013; Rahe et al., 2014). Although there are fewer studies, a relationship between

diet and depression in child and adolescent populations has also been observed. In a recent systematic review, cross-sectional relationships between unhealthy dietary patterns and poorer mental health were consistently found (O'Neil et al., 2014). These findings are particularly concerning given the high consumption of unhealthy food items such as soft drinks and highly-processed foods in paediatric populations (Han and Powell, 2013; Nickelson et al., 2014). While correlation does not confirm causation, findings from longitudinal studies (Le Port et al., 2012) and initial positive findings from dietary interventions (Opie et al., 2014) suggest a causal influence of diet on mood.

Although further investigation is essential, many nutritional and herbal ingredients have confirmed efficacy for the treatment of mild-to-moderate depression in adult populations. In particular, natural supplements such as St John's wort (Linde et al., 2005), S-adenosylmethionine (S-AMe) (Papakostas, 2009), omega 3 polyunsaturated fatty acids (PUFAs) (Grosso et al., 2014b; Sublette et al., 2011) and zinc (Lai et al., 2012) have antidepressant benefits in adults. Investigations on the antidepressant effects of nutritional and herbal treatments for paediatric depression are less common, although have the potential to build upon current treatments. As they are also commonly associated with better safety profiles than pharmaceutical medications, they have garnered significant interest by the general community and parents of depressed youths (Lanski et al., 2003).

The aims of this article are to (i) review epidemiological studies examining the relationship between individual nutrient status and paediatric depression, and (ii) review studies examining the antidepressant effects of various nutritional supplements in paediatric populations. In particular, the following are reviewed: omega-3 polyunsaturated fatty acids (PUFAs), S-AMe, vitamin C, vitamin D, zinc, iron and B-vitamins. An examination of diet quality in child and adolescent depression is beyond the scope of the paper and has been recently covered in a comprehensive systematic review (O'Neil et al., 2014).

## **Methods**

### **Search Criteria**

The PubMed, Google Scholar, and PsycInfo databases were searched from all years of record until September 2014. Most references were obtained from combinations of the following key terms: "depression", "youth or child or adolescent or pediatric", "vitamin", "S-AMe", "zinc", "iron", and "omega-3". The reference lists of relevant papers were also examined to locate additional studies that were not identified by the database searches.

## Eligibility Criteria

Due to the paucity of studies identified, all human-based studies were included if they examined the effects of the previously mentioned nutrients on youths (children through to adolescents) diagnosed with major depression; or evaluated its effects on depressive or other affective-related symptoms. Studies were included if they consisted of cross-sectional or longitudinal evaluations, and treatment-based studies using either case reviews, open-label designs and randomised, double-blind, placebo controlled designs. Studies were only included if they were published in English.

## Omega 3 polyunsaturated fatty acids and depression

Omega-3 fatty acids are long chain, polyunsaturated fatty acids of plant and marine origin. Flaxseed, hemp, canola, and walnuts are rich sources of alpha-linolenic acid (ALA), while fish is a rich source of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). EPA and DHA are highly unsaturated fatty acids that can be metabolised from ALA although this is considered an inefficient process, with only 10-15% of ALA being metabolised into these components (Ross et al., 2007).

The antidepressant effects of omega-3 PUFAs are believed to be derived from one or several of its biological effects. They are potent anti-inflammatories, decreasing the production of inflammatory eicosanoids from arachidonic acid, and inhibiting the release of pro-inflammatory cytokines (Grosso et al., 2014a). Omega-3 PUFAs also encourage synaptic plasticity, provide neuroprotection, and enhance neurotransmission (Crupi et al., 2013). PUFAs also have an important role in maintaining membrane integrity and fluidity (Parker et al., 2006). In animal studies, omega-3 PUFAs also influence serotonin and dopamine production in the central nervous system (Logan, 2003). The beneficial effects of omega-3 on depression may also occur via its influence on hypothalamus-pituitary-adrenal (HPA) activity and cortisol regulation (Barbadoro et al., 2013; Michaeli et al., 2007).

The antidepressant efficacy of omega-3 PUFAs on adults with major depressive disorder has been confirmed in several recent meta-analyses (Grosso et al., 2014b; Sublette et al., 2011). However, results are inconsistent and seem to be influenced by the preparation and dosage used (Bloch and Hannestad, 2012). In two recent meta-analyses it was revealed that preparations with greater concentrations of EPA compared to DHA had greater antidepressant efficacy. In particular, supplements containing EPA concentrations  $\geq 60\%$  of total EPA + DHA were mainly effective against depression (Sublette et al., 2011). However, DHA likely remains important in depression as increased blood concentrations of DHA, but not EPA following fish oil supplementation has been associated with improvements in depressive symptoms (Meyer et al., 2013; Sinn et al., 2012).

## The association between omega-3 PUFAs and paediatric depression

Research on paediatric and adolescent populations have regularly confirmed that omega-3 concentrations are lower in depressed compared to non-depressed groups. For example, in an adolescent population with SSRI-resistant major depressive disorder, erythrocyte DHA, but not EPA, was significantly lower in patients compared with healthy controls (McNamara et al., 2014). In a study by Pottala *et al.*, (2012) levels of red blood cell EPA+DHA were lower in depressed adolescents compared to non-depressed adolescent controls. Finally, in a cross-sectional study examining dietary intake and depressive symptoms in over 6,500 high school students aged between 12 and 15 years, higher intake of fish, EPA, and DHA were independently associated with a lower prevalence of depressive symptoms in male, but not female adolescents (Murakami et al., 2010b). In contrast to these findings, a non-significant association was found by Oddy *et al.*, (2011). In this study, adolescents had a fasting blood sample taken and completed the Food Frequency Questionnaire to assess dietary fatty acid intake, as well as other dietary factors at age 14. Participants also completed the Beck Depression Inventory for Youth (BDI-Y) at age 14 (N = 1,407) and at age 17 (N = 995). An inverse relationship was observed between intake of omega-3 PUFAs at age 14 and BDI-Y scores at both 14 and 17 years of age. However, after adjusting for caloric intake and other lifestyle confounders, the relationships no longer remained significant.

## Omega-3 PUFAs for the treatment of paediatric depression

The antidepressant effects of fish oil supplementation on youth with major depression are scarce, with only two published studies identified. In a 16-week, randomised, double-blind, placebo-controlled study, 28 children diagnosed with major depression were allocated to either omega-3 or placebo treatment. Children were aged between 6 to 12 years and omega-3 supplementation comprised 1000 mg of fish oil daily (380-400 mg eicosapentaenoic and 180-200 mg docosahexaenoic acid). At least one month's rating were obtained from 20 children (5 drop outs from placebo and 3 from omega-3), which were used for data analysis. Analyses showed highly significant treatment effects for omega-3 on depressive symptoms as measured by the CDRS, Children's Depression Inventory (CDI) and CGI. Among children given omega-3 PUFAs, 7 out of 10 experienced a greater than 50% reduction in CDRS, compared to none on placebo. Four out of 10 children receiving omega-3 PUFAs also met criteria for remission (Nemets et al., 2006).

In a 10-week open-label trial, youth and young adults aged 8 to 24 years (mean age 15 years) with SSRI treatment-resistant depression were randomly allocated into low-dose (2.4 g/d, n=7) or high-dose (16.2 g/d, n=7) fish oil treatment. Low-dose fish oil supplementation comprised 2.4/g day,

consisting of 1.6g of EPA and 0.8g of DHA (four capsules daily); while the high-dose treatment comprised 16.2g/ day consisting of 10.8g of EPA and 5.4g of DHA (two tbsp. liquid / day). A total of 14 patients completed the trial (7 from each group), with 4 drop-outs in the low-dose group (two due to worsening of depressive symptoms) and none from the high-dose group. Depressive symptoms as measured by the CDRS-R decreased significantly in the high-dose group (mean reduction of 40%), and there was a trend of change in the low-dose group (mean reduction of 20%; intention to treat analysis). Symptom remission was observed in 40% of patients in the low-dose group and 100% of patients in the high-dose group. Adverse events included mild-to-moderate severity of headache and gastrointestinal symptoms but this did not lead to a discontinuation in treatment (McNamara *et al.*, 2014).

Preliminary positive support for the antidepressant effects of omega-3 PUFAs for youth depression is provided from the two reviewed studies. However, the open-label design used in the study by McNamara *et al.*, (2014) limit the strength of conclusions that can be made from the study. In contrast, the randomised, double-blind, placebo-controlled study design used by Nemets *et al.*, (2006) provides stronger support for the antidepressant benefits of omega-3 supplementation on youths, although this is tempered by the small sample size. Further investigation on the use of omega-3 PUFAs for the treatment and prevention of youth depression is warranted. The efficacy of varying dosages, EPA/DHA ratios and treatment durations, using larger sample sizes and high-quality methodological study designs are required.

## **SAMe and depression**

SAMe is a naturally occurring compound found throughout the human body. Up to half of the daily intake of the amino acid methionine is used for the synthesis of SAMe, where the liver plays a central role in its homeostasis, biosynthesis and degradation (Braun and Cohen, 2007). SAMe is the major donor of methyl groups required in the methylation of hormones, ribonucleic acids, proteins, phospholipids, catecholamines, and several neurotransmitters implicated in major depression, such as dopamine and serotonin (Carney, 1986).

The antidepressant effects of SAMe in adults with major depressive disorder have been examined in several well-controlled studies with generally positive findings (Papakostas, 2009; Williams *et al.*, 2005b). It is more effective than a placebo and at least as effective as pharmaceutical antidepressants such as escitalopram (Sarris *et al.*, 2014) and imipramine (Pancheri *et al.*, 2002). SAMe is also a promising augmenting agent to traditional antidepressant medications (Papakostas *et al.*, 2010; Turner *et al.*, 2014).



## **SAMe for the treatment of paediatric depression**

Surprisingly little research has been undertaken examining the antidepressant effects of SAMe in paediatric populations. Schaller *et al.*, (2004) reported the effects of SAMe administration on three youths diagnosed with major depressive disorder. SAMe at doses of 400 to 1200 mg/ day was effective in ameliorating depressive symptoms in all three youths aged between 8 and 16 years. The youths were followed up for approximately 6 months, with good maintenance of gains. One youth did experience a relapse in depressive symptoms after SAMe was discontinued but symptoms again subsided when SAMe was reinitiated. SAMe was generally well tolerated, although one youth experienced a minor tremor and slight anxiety at a self-administered dose of 1800 mg/day. These side effects subsided after the dose was reduced (Schaller *et al.*, 2004).

Although the findings from these case reports are positive, there remains little scientific support for the antidepressant effects of SAMe for youth depression. Given the efficacy and positive side effect profile of SAMe for the treatment of adult depression, further investigation is certainly warranted using methodologically robust study designs.

## **Vitamin C and depression**

Through several animal and adult human-based studies, there is preliminary evidence that vitamin C (ascorbic acid) has antidepressant effects. For example, in non-depressed, acutely hospitalised patients, the administration of 1,000 mg of vitamin C was associated with a 34% reduction in mood disturbance (Zhang *et al.*, 2011); and in a follow-up study by the same research group vitamin C reduced mood disturbance by 71% and psychological distress by 51% (Wang *et al.*, 2013).

The exact mechanisms associated with the antidepressant effects of vitamin C are unknown but may be due to its antioxidant and corresponding neuroprotective effects (Moretti *et al.*, 2012a; Moretti *et al.*, 2012b). Vitamin C is also a neuromodulator in the brain, modulating both dopamine- and glutamate-mediated neurotransmission (Rebec and Pierce, 1994). Vitamin C also influences 5-HT<sub>1A</sub> receptor activity (Binfare *et al.*, 2009).

## **Vitamin C for the treatment of paediatric depression**

One study was identified examining the antidepressant effects of vitamin C in a paediatric population. Vitamin C was used as an adjunctive agent for the treatment of children aged 7 to 14 years (mean age 10 years) with major depressive disorder in a six-month, double-blind, placebo-controlled trial. The study group (n=12) were given fluoxetine (10-20 mg/day) plus vitamin C (1000

mg/day) and the control group (n=12) were given fluoxetine (10-20 mg/day) plus placebo. Both groups experienced significantly improved scores on the CDRS, CDI, and CGI. Patients treated for six months with fluoxetine and vitamin C showed a highly significant ( $p < 0.0001$ ) decrease in depressive symptoms compared to the fluoxetine plus placebo group as measured by the CDRS and CDI, but not CGI. These preliminary results suggest that vitamin C may be an effective add-on agent in the treatment of depression in paediatric patients (Amr et al., 2013).

This methodologically robust study design provides preliminary support for the use of vitamin C as an adjunctive agent for the treatment of paediatric depression. However, the sample size was small and therefore requires validation through larger clinical trials. In addition, the use of vitamin C as a stand-alone treatment for major depression requires further investigation.

## **Vitamin D and depression**

There has been significant interest in the role of vitamin D on major depression with numerous studies confirming a relationship between vitamin D deficiency and depression in adult populations (Anglin et al., 2013; Ju et al., 2013). Several recent meta-analyses have also now been published examining the effects of vitamin D supplementation on depressive symptoms in adult populations, demonstrating mostly inconsistent results (Li et al., 2014; Shaffer et al., 2014; Spedding, 2014). These inconsistencies may be attributed to variability in dosages, populations examined, pre-treatment vitamin D status, and differing treatment durations used across studies. In a meta-analysis on only studies where (i) vitamin D supplementation was associated increases in post-intervention vitamin D status; (ii) baseline vitamin D level was measured in participants; and (iii) baseline vitamin D level indicated insufficiency, Spedding (2014) concluded that vitamin D supplementation ( $\geq 800$  I.U. daily) was effective for the management of depression with the effect size comparable to that of antidepressant medication.

Vitamin D has several potential antidepressant mechanisms of action. For example, vitamin D can regulate serotonin synthesis by activating the transcription of the serotonin-synthesising enzyme, tryptophan hydroxylase 2 (Patrick and Ames, 2014), and can influence dopamine production via its effect on the expression of the enzymes catechol-O-methyl transferase and tyrosine hydroxylase (Kesby et al., 2009). Vitamin D also influences the body's immune system by modulating the innate and adaptive immune systems, affecting the production of important endogenous antimicrobial peptides and regulating the inflammatory cascade (Arnson et al., 2007; Gunville et al., 2013). Vitamin D can also affect HPA regulation through its influence on glucocorticoid action and glucocorticoid

receptor sensitivity (Obradovic et al., 2006; Zhang et al., 2013). Finally, in animal studies, vitamin D depletion is also associated with altered neurogenesis (Cui et al., 2007; Zhu et al., 2012).

## The association between vitamin D and paediatric depression

In a cross-sectional study on 38 youths with cystic fibrosis aged 7-17 years, serum vitamin D was negatively associated with CDI scores. Furthermore, the group of patients with insufficient vitamin D levels reported significantly more depressive symptoms (Smith et al., 2014). In a prospective cohort study, serum vitamin D<sub>2</sub> and D<sub>3</sub> concentrations were measured at a mean age of 9.8 years and depressive symptoms assessed with the Mood and Feelings Questionnaire (MFQ) at the mean ages of 10.6 years (n = 2,759) and 13.8 years (n = 2,752). Higher concentrations of vitamin D<sub>3</sub> at a mean age 9.8 years were associated with lower levels of depressive symptoms at age 13.8 years (adjusted risk ratio: 0.90), but not at age 10.6 years. Higher concentrations of serum vitamin D<sub>3</sub> were also associated with decreasing depressive symptoms between ages 10.6 and 13.8 years (adjusted RR :1.08). Serum concentrations of vitamin D<sub>2</sub> were not associated with depressive symptoms (Tolppanen et al., 2012).

## Vitamin D for the treatment of paediatric depression

One study was identified examining the antidepressant effects of vitamin D supplementation with youths. Serum vitamin D levels in 54 Swedish, depressed adolescents were measured and participants with vitamin D deficiency were then given vitamin D<sub>3</sub> for 3 months (n = 48). To evaluate well-being and symptoms related to depression and vitamin D status, the WHO-5 well-being scale, the MFQ, and a vitamin D deficiency scale were used. Basal vitamin D levels correlated positively with well-being. After vitamin D supplementation, well-being significantly increased and there were significant improvements in eight of the nine items on the vitamin D deficiency scale (depressed feeling, irritability, tiredness, mood swings, sleep difficulties, weakness, ability to concentrate, and pain). There was also a significant amelioration of depressive symptoms based on the MFQ (Hogberg et al., 2012).

Although findings from this study provide some support for the use of vitamin D for the treatment of paediatric depression, conclusions are limited by the poor study design. Further methodologically robust clinical trials using larger sample sizes, with clinically diagnosed depressed youths are required. Issues around optimal treatment dosages, treatment duration, and baseline cut-off values to begin supplementation also require exploration.

## **Zinc and depression**

There is a growing body of evidence confirming an association between zinc status and adult depression. In a recent meta-analysis it was concluded that a lower blood concentration of zinc was associated with adult depression (Swardfager et al., 2013a). There is also evidence that zinc supplementation as an adjunctive treatment to antidepressant medication enhances treatment gains and reduces symptoms amongst antidepressant-resistant individuals (Lai et al., 2012).

Zinc has numerous essential functions in the body with highest concentrations in the hippocampus and amygdala (Takeda and Tamano, 2009). The antidepressant effects of zinc may be derived by one or a combination of its several biological mechanisms. Zinc protects against oxidative stress, enhances neuroplasticity and neurogenesis, modulates NMDA receptor activity, influences serotonin receptor activity, and moderates immune activity (Swardfager et al., 2013b). Zinc is also an essential cofactor for several nutrients and more than 100 enzymatic reactions in the body (Plum et al., 2010).

### **Zinc for the treatment of paediatric depression**

One study was identified examining the antidepressant effects of zinc in a paediatric population. In a 6-month, randomised, double-blind, placebo-controlled trial, the mental health effects of zinc supplementation (10 mg of zinc oxide) with a placebo on 674 school-aged children were examined. At the completion of the study, there were no differences between the zinc and placebo groups on any behavioural measure. Interestingly, serum zinc concentrations increased in both groups, although larger increases occurred in zinc-supplemented children. Increases in serum zinc concentrations over the course of treatment were associated with decreases in depressive, anxiety, and internalising symptoms (DiGirolamo et al., 2010).

Although findings from this study suggest no overall antidepressant effect of zinc supplementation in a paediatric population, it seems that increases in serum zinc concentrations are necessary for mood improvements. Therefore it is possible that zinc supplementation is only beneficial for children with low baseline zinc stores. Questions around dosages and the most optimal zinc source require further consideration. The antidepressant effects of zinc supplementation on youths diagnosed with depression, in a randomised, double-blind, placebo controlled study is also needed.

## **Iron and depression**

Iron has numerous important biological functions in the body. In the brain iron affects several enzymes involved in oxidative and amino acid metabolism, thereby influencing neurotransmitter

and neuromodulator function (Sachdev, 1993). It is important for dopamine (D<sub>2</sub>) receptor function and has important roles in the function of other neurotransmitters such as serotonin,  $\gamma$ -aminobutyric acid and catecholamines (Beard et al., 1993; Youdim and Green, 1978).

The relationship between iron and depression in adult populations is inconsistent, and this may be partly attributed to significant variability in populations studied. For example, depressive symptoms and iron status were lower in men (Baune et al., 2006; Yi et al., 2011), older age adults (Stewart and Hirani, 2012), and young adult, female students (Vahdat Shariatpanaahi et al., 2007). However, no association was found in premenopausal women (Hunt and Penland, 1999) and iron levels were not associated with the onset of post-partum depression (Armony-Sivan et al., 2012). The antidepressant benefits of iron supplementation on adults are scarce and are again, inconsistent with both positive (Verdon et al., 2003) and negative (Vaucher et al., 2012) findings.

## The association between iron and paediatric depression

Two studies were identified examining the relationship between iron status and depressive symptoms in children. In a longitudinal study, Lozoff *et al.*, (2000) evaluated children aged 11 to 14 years who had been tested for iron deficiency as infants. Children who had severe, chronic iron deficiency in infancy scored lower on mental and motor functioning. Parents and teachers also rated their behaviour as more problematic in several areas including symptoms of anxiety and depression.

Utilising the Taiwan national health insurance database, 2957 children and adolescents with a diagnosis of iron deficiency anaemia were identified and compared with age and gender-matched controls. Iron-deficiency anaemia was associated with an increased risk of unipolar depressive disorder (odd-ratio - OR = 2.34) and other psychiatric disorders such as bipolar disorder (OR = 5.78), anxiety disorder, (OR = 2.17), and attention deficit hyperactivity disorder (OR = 1.67) (Chen et al., 2013).

## Iron for the treatment of paediatric depression

One study was identified investigating the effects of iron supplementation on mental health and affective function. Healthy infants free of iron deficiency anaemia at age 6 months were randomly assigned to iron supplementation or no added iron (formula with iron/powdered cow's milk, vitamins with/without iron) from ages 6 to 12 months. At age 10 years, 59% (666 of 1123) and 68% (366 of 534) of iron-supplemented and no-added-iron groups, respectively were available for follow-up assessments. Examiners blinded to treatment conditions rated the iron-supplemented group as more cooperative, confident, persistent after failure, coordinated, and more respondent to praise,

compared with the no-added-iron group. In a task designed to elicit positive affect, supplemented children started smiling more quickly and spent more time laughing and smiling together with their mothers. In a social stress task they smiled and laughed more and needed less prompting to complete the task. There were no differences in behaviours related to behavioural inhibition, such as anxiety/depression or social problems (Lozoff et al., 2014).

Although little conclusion can be made from this study about the use of iron as a treatment for paediatric depression, it suggests that sufficient iron stores early in life may be beneficial for mood and cognitive functioning later in life. The benefits of iron supplementation in iron-deficient, depressed youths requires investigation in high-quality clinical studies.

## **B-vitamins and depression**

An increasing body of evidence has implicated a role for B-vitamins in adult depression. Folic acid (vitamin B<sub>9</sub>) deficiency is associated with depressive symptoms (Gilbody et al., 2007) and supplementation has demonstrated antidepressant efficacy (Taylor et al., 2004). Deficiencies in vitamins B<sub>12</sub> (Skarupski et al., 2010) and B<sub>6</sub> (Merete et al., 2008; Nanri et al., 2013) have also been implicated in adult depression although well-controlled studies on their antidepressant effects following supplementation are limited with mixed findings (Williams et al., 2005a).

B-vitamins play a central role in energy metabolism, mitochondrial function, and neurotransmitter production (Woolf and Manore, 2006). Folic acid, vitamins B<sub>6</sub> and B<sub>12</sub> are important cofactors in the methylation cycle (Bottiglieri, 2005). Vitamin B<sub>6</sub> is also an essential cofactor for tryptophan metabolism and facilitates the conversion of tryptophan to the neurotransmitter, serotonin (Bernstein, 1990).

## **The association between B-vitamins and paediatric depression**

In adolescent populations, B-vitamin intake was associated with depressive symptoms in two cross-sectional analyses. In a study on 6,500 male and females aged 12 to 15 years, folate and vitamin B<sub>6</sub> intake were inversely associated with depressive symptoms in both sexes. An inverse association between riboflavin (vitamin B<sub>2</sub>) and depression was also found in females only, although there was no identified association with vitamin B<sub>12</sub> status for either sex (Murakami et al., 2010a). In another study using data from 835 respondents, aged 17 years, reduced intake of vitamin B<sub>6</sub> and folate were associated with higher internalising (withdrawn/depressed) behaviour scores as measured by the Youth Self Report (YSR). This association remained even after controlling for a range of confounders

including family income, physical activity, body mass index, and maternal mental health (Herbison et al., 2012).

## **B-vitamins for the treatment of paediatric depression**

No treatment studies were identified examining the antidepressant effects of individual or combination B-vitamins in paediatric populations. However, the mood and behavioural effects of a multivitamin with high-dose B-vitamins has been examined. In this open-label study, the potential efficacy of a multi-nutrient supplement (E.M.Power+) for children with mood and behavioural problems was examined. All children were clinically diagnosed with an anxiety, mood, or behavioural disorder by the referring clinician and were on a stable psychiatric medication regimen. A total of 11 youths, aged between 8 and 15 years old completed this 8 week trial, with outcome measures including the parental completion of the Child Behavior Checklist (CBCL), Youth Outcome Questionnaire (YOQ), and Young Mania Rating Scale (YMRS). Intent-to-treat analyses revealed significance decreases on the YOQ and the YMRS from baseline to final visit. For the 9 completers improvement was significant on seven of the eight CBCL scales, the YOQ, and the YMRS. All effect sizes were large (greater than 0.8) and supplementation was well tolerated (two children reported episodes of vomiting and nausea) (Kaplan et al., 2004).

While this study points to the positive behavioural and mental health effects of multivitamin supplementation with high-dose B-vitamins, it is limited by the uncontrolled study design and non-specific inclusion and exclusion criteria. The multi-nutrient supplement also prevents conclusions about the antidepressant benefits of individual B-vitamins and other nutrients.

## **Conclusions and recommendations for future research**

From this narrative review on studies investigating nutrients for the treatment of paediatric depression it appears that there are several promising options. However, there is a lack of high-quality, randomised, double-blind, placebo-controlled study designs. Only 4 studies were identified utilising this 'gold standard' research design. These include one study investigating the following nutrients; omega-3 PUFAs (Nemets et al., 2006), vitamin C (Amr et al., 2013), zinc (DiGirolamo et al., 2010), and iron (Lozoff et al., 2014). Unfortunately, these studies were compromised by small sample sizes and/or included participants with a lack of clearly defined major depression. Given the impact that depression has on the social, psychological, and educational function of a child, and the greater risk of depressive episodes into adulthood, further research on treatment and prevention options are certainly necessary.

Currently, the primary interventions for paediatric depression comprise psychological therapies and pharmaceutical medications. These treatments are far from perfect and there remain significant concerns about the use of pharmaceuticals in youths. Nutrient therapies comprising either individual or combination formulas present as potential treatment options. As depression is associated with several psychological, social, biological and lifestyle causes, individual nutrients are unlikely to be a panacea for the epidemic of depression in adult and paediatric populations; however, they present as alternative, adjuvant natural options to enhance current treatment outcomes.

Given the limited data on nutrient therapies in paediatric populations, there are several areas that require further examination. Some of these include:

- What dosages are required for children and how do these vary from early childhood through to adolescence?
- Does the efficacy of differing nutrients and respective dosages vary across gender?
- Do single or combined-nutrient formulas provide greater antidepressant effects?
- How effective are nutrients as stand-alone and/or adjunct treatments to psychological, pharmaceutical and other therapeutic options?
- What are the interactions between these supplements and pharmaceutical medications?
- How safe are these natural supplements for youth, how do they vary with differing dosages, and how do the frequency of adverse events compare to pharmaceuticals?
- Can these ingredients be delivered in powdered or liquid formulations to increase compliance particularly in younger children?
- How effective is nutrient supplementation for the prevention of major depression in youths?
- What is the efficacy of nutrient therapies in clinically diagnosed depressed youths compared to youth with depressive/ affective symptoms?

In addition, although individual nutrients were only covered in this review, there are several herbal ingredients that have antidepressant properties and present as potential options for the treatment of paediatric depression. The most-recognised herbal antidepressant, St John's wort (*Hypericum perforatum*), has received scant attention in paediatric populations. Findings from three open-label studies have been promising (Findling et al., 2003; Hubner and Kirste, 2001; Simeon et al., 2005), but require validation through greater controlled, robustly-designed studies on clearly defined populations. Examples of other potential herbal options include *Crocus sativus* (saffron), *Lavandula angustifolia* (lavender), and *Rhodiola rosea*. Curcumin, derived from the Indian spice turmeric, has received increasing attention for the treatment of adult depression (Lopresti et al., 2014), and presents as another promising option requiring investigation. Given the importance of digestive



function for nutrient absorption and evidence of increased gut permeability in adult depression (Maes et al., 2012), probiotics presents as another potential option and has received increased attention in psychiatry (Slyepchenko et al., 2014).

As demonstrated in this review, paediatric depression is also associated with deficiencies in several nutrients. However, replenishment through simple supplementation of individual nutrients fails to treat potential causes of these deficiencies. These include issues around a child's diet quality, digestive-related issues (e.g., coeliac disease, food intolerances, intestinal hyperpermeability, and intestinal dysbiosis), and chronic stress which can influence digestive function. Awareness of these causes should therefore form a component of any treatment formulation for major depression.

Paediatric depression is a debilitating disorder that can lead to significant impairment throughout a person's life. Therefore, efforts at investigating novel therapies to enhance current treatment efficacy rates are required. Nutritional therapies present as promising treatment options but require greater investigation through robust study designs before they can be recommended as first-line treatments options for paediatric depression.

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